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REVERSE CHEMOSELECTIVE BORANE REDUCTION OF AN OPTICALLY ACTIVE MALONIC ACID ESTER

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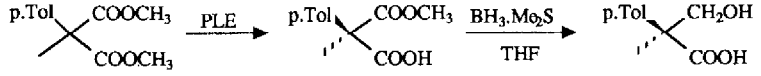
Summary : Reduction of the 2-methyl-2-p-tolylmalonic monoester (+)-**2** with the borane-dimethylsulfide complex took place unexpectedly on the ester function,providing the β-hydroxy-acid (-)-**3**. This chemoselective reaction proceeded likely through formation of a six-membered ring monoacyloxyborane intermediate **6a** and intramolecular hydride transfer.

Usually,carboxylic acids are readily reduced by borane [1,2], while carboxylic esters are selectively reduced by lithium borohydride or sodium in ammonia [3,4]. A recent report concerning the borane reduction of phenylmalonic acids into 1,3-propanediols [5] prompts us to disclose our unexpected results in this field. Our current investigation concerning the preparation of optically active succinates [6] as efficient precursors of cyclopropane derivatives, which provide valuable building blocks for the total synthesis of natural compounds [7], requires large amounts of β-hydroxy propionic acid derivatives such as **3**, for instance.

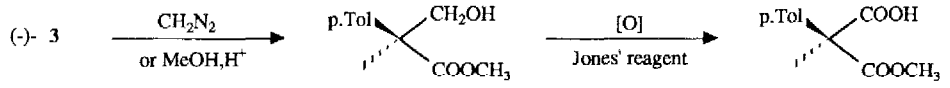


(R,S)- **1** (+)- **2** (-)- **3**

Successive alkylation of commercially available methyl p-tolylacetate by methyl iodide and methyl chloroformate using LDA as basic reagent, gave the racemic methyl malonate (R,S)-**1** in 78% yield after liquid chromatography. Enantioselective enzymatic hydrolysis by pig liver esterase (PLE) [8], following a known procedure [9] transformed the diester **1** into the chiral acid ester (+)-(R)-**2** ($[\alpha]_D$ = +12°, c = 1, $CHCl_3$) [10] with 96% enantiomeric excess, determined from 250 MHz ^1H n.m.r. spectra of the salt of **2** with (+)-(R)-α-methylbenzylamine, comparatively to the spectra recorded from the ammonium salt of the racemic acid ester **2** [11]. As previously reported, the enantioselectivity is dependent upon the substitution pattern at the chiral center of the malonate **1**: the more different the size of the substituents, the higher is the enantiomeric excess [9a]; the R absolute configuration of the acid ester (+)-**2** was assigned analogously to reported data [9c].

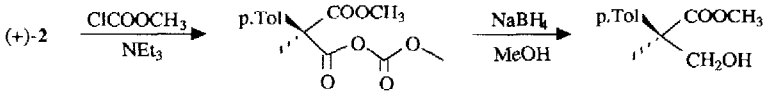
It has been reported that the reduction of phenylmalonic acid by borane in THF is slow comparatively to other carboxylic acids, providing 2-phenyl 1,3-propanediol in 35% yield only on reaction for 16 h at 0°C ; furthermore, use of borane-dimethylsulfide (BH_3-Me_2S) did not enhance the yield of reduction [5]. On the other

hand, reduction of the optically active acid ester (+)-**2** with BH_3-Me_2S was performed at 0°C or 20°C in THF, within 1 h, and provided unexpectedly the β-hydroxyacid (-)-**3** (85%).



(-)- **4** (-)- **2**

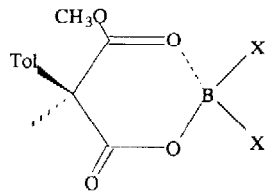
Esterification of the β-hydroxyacid (-)-**3** with diazomethane or with MeOH (cat. $SOCl_2$) led to the β-hydroxyester (-)-4 ([α] = -57°, c = 1, $CHCl_3$) ; then, oxidation with Jones'reagent gave the enantiomeric monoester (-)-**2** ([α] = -12°, c = 1, $CHCl_3$), in 86% yield.



5 (+)-**4**

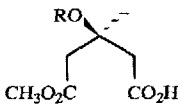
Reaction of the acid ester (+)-**2** with one equiv. of methyl chloroformate in THF at 0°C in the presence of 1.1 equiv. of NEt_3[12] gave the anhydride **5**, which was directly reduced by $NaBH_4$ in methanol into the enantiomeric β-hydroxy ester (+)-**4** ([α] = +60°, c = 1, $CHCl_3$) [13], in 70% overall yield.

In order to explain the abnormal behaviour of the acid ester (+)-**2**, *i.e.*, the preferred borane reduction of the ester function in presence of a carboxylic acid group, we have considered the formation of a six-membered ring intermediate **6a.**

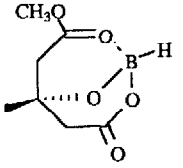


6a X=H
6b X=Sia

Effectively, it has been previously reported that the reaction of carboxylic acids that are not reduced by borane-THF stops at a bis (acyloxy) borane intermediate [14] ; and a cyclic (phenylmalonyldioxy) borane has been isolated and characterized [5, 15]. On the other hand, no reduction occurred upon treatment of the acid ester (+)-**2** with the $HB(Sia)_2$-Me_2S complex, although the cyclic intermediate **6b** was likely formed, but with no transferable hydride. Addition of an excess of BH_3-Me_2S or treatment of **6b** with $NaBH_4$ in MeOH at 20°C (i.e., with a more nuleophilic hydride) [16] did not give rise to the reduction product **3** ; otherwise, partial decarboxylation was observed which increased upon heating at 40°C to give racemic methyl 2-p-tolyl propionate. From these results it can be concluded that borane reduction of the activated ester group of (+)-**2** involved an intramolecular hydride transfer within the cyclic intermediate **6a.**



7a R=H
7b R=Ac



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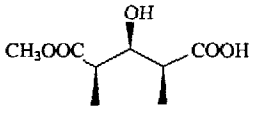
A related reaction, the unexpected borane (BH_3-Me_2S) reduction of the ester moiety of the 3-hydroxy glutaric monoester **7a** previously reported [17], is likely due to the presence of the β–hydroxy group allowing formation of the six-membered ring complex **8** [18] and intramolecular hydride transfer to the activated ester ; acetylation of the hydroxy group prevents the six-membered ring **8** to form and allows normal borane selective reduction of the acidic carboxyl group of **7b** to occur.



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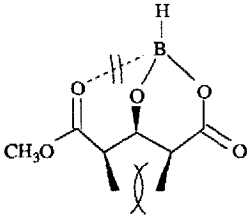

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On the other hand, the recently reported exclusive normal reduction with $BH_3.Me_2S$ in THF at 0°C of the carboxylic acid of monomethyl 3-hydroxy-2,4-dimethyl glutarate **9** [19] could then explained by the steric hindrance of the two methyl groups which prevents the formation of any intermediate cyclic complex such as **10** and therefore carboxyl ester group activation [20].

In conclusion, the reverse chemoselective borane reduction of carboxylic ester in the presence of a carboxylic acid can be obtained only when a six-membered ring complex is formed, allowing an intramolecular hydride transfer.

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10) (+)-**2** : IR (neat) : 3220, 1735, 1712 cm^{-1} ; ^{1}H-NMR 250 MHz ($CDCl_3$) : 9.1 (s, H), 7.38 (d, 2H), 7.18 (d, 2H), 3.79 (s, 3H), 2.35 (s, 3H), 1.90 (s, 3H) ; ^{13}C-NMR ($CDCl_3$) : 176.4 (s), 172.5 (s), [6 arom. c : 137.5 (s), 134.5 (s), 129.1 (d), 127.0 (2d)], 58.3 (s), 53.0 (q), 21.6 (q), 20.3 (q).

11) Racemic monoester **2** was prepared by successive alkylation of methyl p-tolylacetate by methyl iodide and gaseous CO_2 using LDA as basic reagent.

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13) (+)-**4** : IR (neat) : 3450, 1735, 1620, 1580 cm^{-1} ; ^{1}H-NMR 250 MHz ($CDCl_3$) : 7.18 (b,s, 4H), 3.83 (AB, $\Delta\upsilon_{AB}$ = 112.5 Hz, J_{AB} = 11.5 Hz, 2H), 3.73 (s, 3H), 2.42 (s, OH), 2.35 (s, 3H), 1.65 (s, 3H) ; ^{13}C-NMR ($CDCl_3$) : 176.7 (s), [6 arom. c : 137.3 (s), 137.0 (s), 129.3 (2d), 126.0 (2d)], 69.7 (t), 52.2 (q), 52.2 (s), 20.9 (q), 20.0 (q). M.S. m/e (rel. int.) : 208 (M^+, 0.5), 178 (79), 149 (32), 146 (50), 119 (100), 118 (29), 117 (76), 91 (52), 77 (19).

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